

SEQUENCE LISTING

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<120> MODULATION OF EPIDERMAL GROWTH FACTOR HETERODIMER ACTIVITY

<130> 421/99 PCT

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<151> 2004-02-17

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 Thr Pro Gln His Val Lys Ile Thr Gly Phe Gly Leu Ala Lys Leu Leu
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 Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln
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 Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp
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 Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg
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 Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro
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 Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
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 Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
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 Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
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 Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
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 Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
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 Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
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 Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
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 Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
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 Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
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gcc cgc tgc aag ggg cca ctg ccc act gac tgc tgc cat gag cag tgt Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys 225 230 235 240			958
gct gcc ggc tgc acg ggc ccc aag cac tct gac tgc ctg gcc tgc ctc Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu 245 250 255			1006
cac ttc aac cac agt ggc atc tgt gag ctg cac tgc cca gcc ctg gtc His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val 260 265 270			1054
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450	455	460	
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ccc tgg gac cag ctc ttt cgg aac ccg cac caa gct ctg ctc cac act Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr 485 490 495			1726
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cct ccc ttc tgc gtg gcc cgc tgc ccc agc ggt gtg aaa cct gac ctc Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu 595 600 605			2062
tcc tac atg ccc atc tgg aag ttt cca gat gag gag ggc gca tgc cag Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln 610 615 620			2110
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Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile	740	745	750	
aaa gtg ttg agg gaa aac aca tcc ccc aaa gcc aac aaa gaa atc tta				2542
Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu	755	760	765	
gac gaa gca tac gtg atg gct ggt gtg ggc tcc cca tat gtc tcc cgc				2590
Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg	770	775	780	
ctt ctg ggc atc tgc ctg aca tcc acg gtg cag ctg gtg aca cag ctt				2638
Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu	785	790	795	800
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Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg	805	810	815	
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Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly	820	825	830	
atg agc tac ctg gag gat gtg cgg ctc gta cac agg gac ttg gcc gct				2782
Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala	835	840	845	
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Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe	850	855	860	
ggg ctg gct cgg ctg ctg gac att gac gag aca gag tac cat gca gat				2878
Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp	865	870	875	880
ggg ggc aag gtg ccc atc aag tgg atg gcg ctg gag tcc att ctc cgc				2926
Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg	885	890	895	
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Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val	900	905	910	
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Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala	915	920	925	
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Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro	930	935	940	
ccc atc tgc acc att gat gtc tac atg atc atg gtc aaa tgt tgg atg				3118
Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met	945	950	955	960
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Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe	965	970	975	
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Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu	980	985	990	
gac ttg ggc cca gcc agt ccc ttg gac agc acc ttc tac cgc tca ctg				3262
Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu				

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ggt gcc gtg gag aac ccc gag Gly Ala Val Glu Asn Pro Glu 1190	tac ttg aca ccc cag Tyr Leu Thr Pro Gln 1195	gga gga gct Gly Gly Ala 1200	3847
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ccc agc acc ttc aaa ggg aca Pro Ser Thr Phe Lys Gly Thr 1235	cct acg gca gag aac Pro Thr Ala Glu Asn 1240	cca gag tac Pro Glu Tyr 1245	3982
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1250

1255

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35 40 45

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Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
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Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
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Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
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Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
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Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
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 Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
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 Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
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 His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
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 Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
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 Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
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 Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
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 370 375 380
 Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
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 Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg

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 465 470 475 480
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 Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
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 530 535 540
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 Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
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 Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
 580 585 590
 Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
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 Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
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 625 630 635 640
 Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser
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 Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly
 660 665 670
 Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
 675 680 685
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690

695

700

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Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
725 730 735

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Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
755 760 765

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
770 775 780

Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
785 790 795 800

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805 810 815

Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
820 825 830

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850 855 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
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885 890 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
900 905 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala
915 920 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro
930 935 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
945 950 955 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe

965

970

975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu
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Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu
 995 1000 1005

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr
 1010 1015 1020

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Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro Leu Pro
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Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Pro Lys Thr Leu
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Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val Phe Ala Phe Gly
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Gly Ala Val Glu Asn Pro Glu Tyr Leu Thr Pro Gln Gly Gly Ala
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Met Glu Leu Ala Ala Trp Cys Arg Trp Gly Phe Leu Leu Ala Leu Leu
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Ser Pro Gly Ala Ala Gly Thr Gln Val Cys Thr Gly Thr Asp Met Lys
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Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
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ctc tac cag ggc tgt cag gtg gtg cag ggc aat ttg gag ctt acc tac 371
Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
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Gln Gly Tyr Met Leu Ile Ala His Asn Arg Val Lys His Val Pro Leu
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Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Lys Tyr
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cta agg aag ctg aag gtg ctt ggg tca gga gcc ttc ggc act gtc tac Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr 725 730 735			2387
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Pro Glu Val Arg Pro Gln Ser Pro Leu Thr Pro Glu Gly Pro Pro				
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Thr Ala Ser Gln Pro His Pro Ser Pro Ala Phe Ser Pro Ala Phe				
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 Tyr Leu Gly Leu Asp Val Pro Val
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Leu Pro Ala Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
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Gln Gly Tyr Met Leu Ile Ala His Asn Arg Val Lys His Val Pro Leu
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Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Lys Tyr
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Ala Leu Ala Val Leu Asp Asn Arg Asp Pro Leu Asp Asn Val Thr Thr
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Ala Ala Pro Gly Arg Thr Pro Glu Gly Leu Arg Glu Leu Gln Leu Arg
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Gln Leu Cys Tyr Gln Asp Met Val Leu Trp Lys Asp Val Leu Arg Lys
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Asn Asn Gln Leu Ala Pro Val Asp Met Asp Thr Asn Arg Ser Arg Ala
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Cys Pro Pro Cys Ala Pro Thr Cys Lys Asp Asn His Cys Trp Gly Glu
195 200 205

Ser Pro Glu Asp Cys Gln Ile Leu Thr Gly Thr Ile Cys Thr Ser Gly
210 215 220

Cys Ala Arg Cys Lys Gly Arg Leu Pro Thr Asp Cys Cys His Glu Gln
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Cys Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys
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Leu His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu
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Ile Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Leu Asn Pro Glu Gly
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Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr Thr Cys Pro Tyr Asn Tyr
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 Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly
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 Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp
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 Val Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His
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 Ser Gly Asn Arg Pro Glu Glu Ala Cys Gly Leu Glu Gly Leu Val Cys
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 Asn Ser Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln
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 Asp Ser Ser Ser Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp
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Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr
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Ile Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile
 755 760 765

Leu Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser
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Arg Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln
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Arg Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Val Gln Ile Ala Lys
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Gly Met Ser Tyr Leu Glu Glu Val Arg Leu Val His Arg Asp Leu Ala
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Asp Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu
885 890 895

Arg Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr
900 905 910

Val Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro
915 920 925

Ala Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln
930 935 940

Pro Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp
945 950 955 960

Met Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu
965 970 975

Phe Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn
980 985 990

Glu Asp Leu Gly Pro Ser Ser Pro Met Asp Ser Thr Phe Tyr Arg Ser
995 1000 1005

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Tyr Leu Val Pro Gln Gln Gly Phe Phe Ser Pro Asp Pro Ala Leu
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Glu Glu Pro Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly
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Ser Asp Val Phe Asp Gly Asp Leu Ala Val Gly Val Thr Lys Gly
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Leu Gln Ser Leu Ser Pro His Asp Leu Ser Pro Leu Gln Arg Tyr
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Ser Glu Asp Pro Thr Leu Pro Leu Pro Pro Glu Thr Asp Gly Tyr
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Val Ala Pro Leu Ala Cys Ser Pro Gln Pro Glu Tyr Val Asn Gln
1130 1135 1140

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 Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Glu Ser Cys Gln Glu
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 Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser
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 Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly
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 Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg
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Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile
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Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala
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gcc cgg ggt tcc gag atg ggc aac tct cag gca gta tgt cct ggg act 96
Ala Arg Gly Ser Glu Met Gly Asn Ser Gln Ala Val Cys Pro Gly Thr
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cta aac ggg ctg agt gtg acc ggc gat gct gac aac cag tac cag aca 144
Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Asp Asn Gln Tyr Gln Thr
35 40 45

ctg tac aaa ctc tat gag aag tgt gag gtg gtc atg ggt aac ctg gag 192
 Leu Tyr Lys Leu Tyr Glu Lys Cys Glu Val Val Met Gly Asn Leu Glu
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 Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile
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cga gaa gtg aca ggc tat gta ctg gtg gcc atg aat gaa ttc tct gta 288
 Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Val
 85 90 95

ctg ccc tta cct aac ctc cga gtg gtc cgg gga acc cag gtc tac gat 336
 Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp
 100 105 110

ggg aag ttt gcc atc ttt gtc atg ttg aac tac aat acc aac tcc agc 384
 Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser
 115 120 125

cat gct ctg cgc cag ctc cgg ttc act cag ctt act gag att ctg tta 432
 His Ala Leu Arg Gln Leu Arg Phe Thr Gln Leu Thr Glu Ile Leu Leu
 130 135 140

ggg ggc gtt tac att gag aag aat gac aaa ctt tgc cac atg gat aca 480
 Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr
 145 150 155 160

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 Ile Asp Trp Arg Asp Ile Val Arg Val Pro Asp Ala Glu Ile Val Val
 165 170 175

aag aac aac ggg ggg aac tgt cca ccc tgt cac gaa gtc tgc aag ggg 576
 Lys Asn Asn Gly Gly Asn Cys Pro Pro Cys His Glu Val Cys Lys Gly
 180 185 190

cga tgc tgg ggg cct gga cca gaa gac tgc cag ata ttg acc aag acc 624
 Arg Cys Trp Gly Pro Gly Pro Glu Asp Cys Gln Ile Leu Thr Lys Thr
 195 200 205

atc tgt gcc cct cag tgt aac ggt cgc tgc ttc ggg ccc aat cct aac 672
 Ile Cys Ala Pro Gln Cys Asn Gly Arg Cys Phe Gly Pro Asn Pro Asn
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cag tgc tgc cac gat gaa tgt gca ggt ggc tgc tct gga ccc cag gac 720
 Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp
 225 230 235 240

aca gat tgc ttc gcc tgc cga cac ttc aat gac agt ggt gcc tgt gtg 768
 Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val
 245 250 255

ccc agg tgt cca gcg ccc ctt gtg tac aac aag cta acg ttc cag ctt 816
 Pro Arg Cys Pro Ala Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu
 260 265 270

gag ccc aac ccc cat atc aag tat cag tac gga gga gtc tgt gtt gcc 864
 Glu Pro Asn Pro His Ile Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala
 275 280 285

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 Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Phe Cys Val Arg Ala
 290 295 300

tgt cct gct gac aag atg gaa gta gat aag aat gga ctc aag atg tgt 960
 Cys Pro Ala Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys
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aac tgt acc aag atc ctg ggc aac ctg gac ttc ctc atc act ggc ctc Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu 355 360 365	1104
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acc atc ggg ggc aga agc ctc tac aat cgg ggc ttc tcc ttg ttg atc Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile 420 425 430	1296
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gcc cat ttt cgt gat ggg ccc cac tgt gtg aac agc tgc ccc cat gga Ala His Phe Arg Asp Gly Pro His Cys Val Asn Ser Cys Pro His Gly 580 585 590	1776

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 Ile Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Ala Gln Asn
 595 600 605

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 Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro
 610 615 620

gaa cta caa gac tgt tta ggc caa gca gag gta tta atg agc aaa cca 1920
 Glu Leu Gln Asp Cys Leu Gly Gln Ala Glu Val Leu Met Ser Lys Pro
 625 630 635 640

cac ctg gtc ata gcg gtg aca gta gga ctg act gtg atc ttc ctg att 1968
 His Leu Val Ile Ala Val Thr Val Gly Leu Thr Val Ile Phe Leu Ile
 645 650 655

ctg gga ggc tct ttt ctc tat tgg cgt gga cgc agg att cag aat aaa 2016
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agg gct atg aga cgc tac ttg gag cgg ggt gag agc atc gag cct ctg 2064
 Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu Pro Leu
 675 680 685

gac cca agc gag aag gca aac aaa gtc ttg gct aga atc ttc aaa gag 2112
 Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe Lys Glu
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 705 710 715 720

gta cac aag ggg att tgg att ccc gag ggt gaa tcc atc aag att cca 2208
 Val His Lys Gly Ile Trp Ile Pro Glu Gly Glu Ser Ile Lys Ile Pro
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 Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser Phe Gln
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cgt gag aca ctg gga cca cag ctg ctg ctc aac tgg gga gta caa att 2448
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gcc aag ggt atg tat tac ctc gag gaa cac agc atg gtg cat agg gac 2496
 Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Ser Met Val His Arg Asp
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cta cac agt gag gcc aag act cca att aaa tgg atg gcc ctt gag agt Leu His Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu Glu Ser 865 870 875 880	2640
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Tyr His	Ser Gln Arg His Ser	Leu Leu Thr Pro Val	Thr Pro Leu	
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Ser Pro	Pro Gly Leu Glu Glu	Glu Asp Gly Asn Gly	Tyr Val Met	
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Pro Asp	Thr His Leu Arg Gly	Thr Ser Ser Ser Arg	Glu Gly Thr	
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Leu Ser	Ser Val Gly Leu Ser	Ser Val Leu Gly Thr	Glu Glu Glu	
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Asp Glu	Asp Glu Glu Tyr Glu	Tyr Met Asn Arg Lys	Arg Arg Gly	
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Tyr Glu	Tyr Met Asp Val Gly	Ser Asp Leu Ser Ala	Ser Leu Gly	
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Ala Gly	Thr Thr Pro Asp Glu	Asp Tyr Glu Tyr Met	Asn Arg Arg	
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Arg Gly	Ala Gly Gly Ser Gly	Gly Asp Tyr Ala Ala	Met Gly Ala	
1265	1270	1275		
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Cys Pro	Ala Ala Glu Gln Gly	Tyr Glu Glu Met Arg	Ala Phe Gln	
1280	1285	1290		
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Gly Pro	Gly His Gln Ala Pro	His Val Arg Tyr Ala	Arg Leu Lys	
1295	1300	1305		
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 Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile
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 Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Val
 85 90 95
 Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp
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 Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser
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 His Ala Leu Arg Gln Leu Arg Phe Thr Gln Leu Thr Glu Ile Leu Leu
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 Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr
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 Ile Asp Trp Arg Asp Ile Val Arg Val Pro Asp Ala Glu Ile Val Val
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 Lys Asn Asn Gly Gly Asn Cys Pro Pro Cys His Glu Val Cys Lys Gly
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 Arg Cys Trp Gly Pro Gly Pro Glu Asp Cys Gln Ile Leu Thr Lys Thr
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 Ile Cys Ala Pro Gln Cys Asn Gly Arg Cys Phe Gly Pro Asn Pro Asn
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 Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp
 225 230 235 240
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 Pro Arg Cys Pro Ala Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu
 260 265 270

Glu Pro Asn Pro His Ile Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala
 275 280 285

Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Phe Cys Val Arg Ala
 290 295 300

Cys Pro Ala Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys
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Glu Pro Cys Arg Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser
 325 330 335

Gly Ser Arg Tyr Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val
 340 345 350

Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu
 355 360 365

Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu
 370 375 380

Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly Tyr Leu Asn Ile Gln
 385 390 395 400

Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr
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Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile
 420 425 430

Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe Arg Ser Leu Lys Glu
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Ile Ser Ala Gly Arg Val Tyr Ile Ser Ala Asn Gln Gln Leu Cys Tyr
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His His Ser Leu Asn Trp Thr Arg Leu Leu Arg Gly Pro Ala Glu Glu
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Arg Leu Asp Ile Lys Tyr Asn Arg Pro Leu Gly Glu Cys Val Ala Glu
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Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro
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Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Glu Gly Val
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Cys Val Thr His Cys Asn Val Leu Gln Gly Glu Pro Arg Glu Phe Val
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His Glu Ala His Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Glu
545 550 555 560

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565 570 575

Ala His Phe Arg Asp Gly Pro His Cys Val Asn Ser Cys Pro His Gly
580 585 590

Ile Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Ala Gln Asn
595 600 605

Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro
610 615 620

Glu Leu Gln Asp Cys Leu Gly Gln Ala Glu Val Leu Met Ser Lys Pro
625 630 635 640

His Leu Val Ile Ala Val Thr Val Gly Leu Thr Val Ile Phe Leu Ile
645 650 655

Leu Gly Gly Ser Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln Asn Lys
660 665 670

Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu Pro Leu
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Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe Lys Glu
690 695 700

Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe Gly Thr
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Val His Lys Gly Ile Trp Ile Pro Glu Gly Glu Ser Ile Lys Ile Pro
725 730 735

Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser Phe Gln
740 745 750

Ala Val Thr Asp His Met Leu Ala Val Gly Ser Leu Asp His Ala His
755 760 765

Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln Leu Val
770 775 780

Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg Gln His
785 790 795 800

Arg Glu Thr Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val Gln Ile
805 810 815

Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Ser Met Val His Arg Asp
820 825 830

Leu Ala Leu Arg Asn Val Met Leu Lys Ser Pro Ser Gln Val Gln Val
835 840 845

Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys Gln Leu
850 855 860

Leu His Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu Glu Ser
865 870 875 880

Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser Tyr Gly
885 890 895

Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr Ala Gly
900 905 910

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915 920 925

Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met Val Lys
930 935 940

Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu Leu Ala
945 950 955 960

Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu Val Ile
965 970 975

Lys Arg Ala Ser Gly Pro Gly Ile Pro Pro Ala Ala Glu Pro Ser Ala
980 985 990

Leu Ser Thr Lys Glu Leu Gln Asp Ala Glu Leu Glu Pro Asp Leu Asp
995 1000 1005

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Leu Gly Ser Ala Leu Ser Leu Pro Thr Gly Thr Leu Thr Arg Pro
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Met Asn Gln Ser Asn Leu Gly Glu Ala Cys Leu Asp Ser Ala Val
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 1115 1120 1125
 Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val Thr Pro Leu
 1130 1135 1140
 Ser Pro Pro Gly Leu Glu Glu Glu Asp Gly Asn Gly Tyr Val Met
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 Pro Asp Thr His Leu Arg Gly Thr Ser Ser Ser Arg Glu Gly Thr
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 1175 1180 1185
 Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Lys Arg Arg Gly
 1190 1195 1200
 Ser Pro Ala Arg Pro Pro Arg Pro Gly Ser Leu Glu Glu Leu Gly
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/04968

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/00; G01N 33/53; A61K 38/00; C07K 1/00, 2/00, 4/00, 5/00, 7/00, 14/00, 16/00, 17/00
US CL : 435/4, 7.1; 530/300, 350, 385, 386, 387.1, 387.3; 436/64, 86

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/4, 7.1; 530/300, 350, 385, 386, 387.1, 387.3; 436/64, 86

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
West and Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROBERTS, R.B. et al. Modeling the cancer pateint with genetically engineered mice: prediction of toxicity from molecule-targeted therapies. February 2004, Vol 5, pages 115-120.	1-28



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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